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Contraceptive methods and the transmission of HIV: implications for family planning

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Abstract

Heterosexual transmission is the predominant mode of spread of the Human Immunodeficiency Virus (HIV) in most of the world. Whether the use of hormonal contraceptives, IUDs and spermicides is associated with an increased or decreased risk for HIV acquisition remains controversial. Several mechanisms whereby contraceptive methods may influence the transmission of HIV have been proposed. As contraceptive use increases among women of reproductive age, the group most vulnerable to HIV infection, any associations between contraceptive method and HIV risk become even more important.

The available studies of these associations are predominantly cross-sectional and give conflicting results. We review the published evidence for associations between HIV and individual contraceptive methods. At this time no definitive conclusions regarding these associations can be drawn. Further research, especially prospective epidemiological studies and basic biological research on mechanisms of heterosexual transmission and the effect of contraceptives on these mechanisms, is urgently needed.

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Introduction

Human Immunodeficiency Virus (HIV) is predominantly acquired through heterosexual transmission and in many parts of the world, HIV prevalence and incidence rates are higher among women than men.[1] Because specific contraceptive methods may increase or decrease a woman's susceptibility to HIV infection given exposure, or her infectivity to her partner if she is already infected with HIV, family planning and HIV control are interrelated. The need for attention to both pregnancy prevention and HIV prevention when recommending a contraceptive method is made even more urgent by the increasing prevalence of modern contraceptive use for family planning in many countries with a high or increasing prevalence of HIV infection.

We review the current literature on HIV transmission and use of oral contraceptives, injectable hormonal contraceptives, IUDs, spermicidal preparations, and the female condom. In view of the repeated calls for assessment of female-controlled methods of HIV prevention which are readily reversible contraceptives,[2,3] we pay particular attention to the latter two. We summarise the remaining substantial research needs and discuss the programme and policy implications of our current level of knowledge of these associations. Reviews of male condom use and HIV transmission appear elsewhere.[4,5]

METHODOLOGIC DIFFICULTIES IN STUDIES OF CONTRACEPTIVE USE AND HIV TRANSMISSION

Study design: Randomised trials of contraceptive methods in human populations are difficult to conduct in a blinded manner and raise substantial ethical concerns. Thus, almost all studies of these issues are observational. Most studies have been cross-sectional or case-control in design and suffer from the major problem that HIV serostatus and past contraceptive use are simultaneously determined. Thus, it is not usually possible to know for any seropositive individual whether they acquired HIV infection before, during, or after contraceptive use.

Prospective studies, in which contraceptive use is ascertained and updated for a group of seronegative individuals who are then monitored for HIV seroconversion, have been few. This is largely due to the logistical difficulties associated with achieving adequate follow-up in populations exposed to HIV, as well as the ethical imperative to attempt to prevent seroconversion through sexual partner reduction or condom use. The prospective studies which have been performed have almost all been among female sex workers; in lower risk groups, thousands of women would have to be followed for several years in order that a large enough number of seroconversions are observed for the studies to have adequate power. The emphasis on high-risk groups however, does raise questions on the generalisability of the results to women in the general population.

Confounding: Since both HIV risk and choice of contraceptive method may be associated with many characteristics, including marital status, age, number of sexual partners, and socioeconomic status, these factors are potential confounders of the relationship between them. Any study of the association between contraceptive use and HIV transmission should carefully control for all potential confounders in the analysis. Since the predominant risk for HIV seroconversion is exposure to HIV itself, behavioural risk factors may have much higher relative risks than biological

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co-factors such as contraceptive use. It is not surprising that the studies to date are conflicting, as the changes in risk ratios due to bias and confounding can potentially be larger than the relative risk due to the exposure itself.

Oral Contraceptives (OCs)

Whether the use of oral hormonal contraceptives is associated with an increased risk for HIV acquisition remains controversial. Because the prevalence of OC use is low in most developing countries, their impact on HIV transmission overall is likely to be minor even in regions of high HIV prevalence. However, because family planning programmes are promoting OC use in many parts of the developing world, any interaction of OC use and HIV transmission deserves careful consideration.

Mechanisms of influence on HIV transmission: Several mechanisms have been proposed that could contribute to a role of OCs in the transmission of HIV:

Cervical ectropion: It is postulated that since areas of ectropion are more vulnerable to trauma than the "normal" squamous epithelium of the ectocervix, cervical ectropion may enhance HIV transmission. Cervical ectropion is frequently observed in women during puberty and pregnancy, as well as among women using OCs. Additionally, it has been observed that cervical ectropion may increase susceptibility to *Chlamydia trachomatis* infection[6] which may in turn increase HIV risk.

Cervical ectropion has been associated with HIV concordance among couples in Nairobi (OR = 5·0, CI 1·7–14·7, p = 0·007).[7] However, the women in this study were identified after seroconversion and therefore it is not possible to be certain that the ectropion was not a consequence of HIV seropositivity. Cervical ectropion and use of OCs was not statistically significantly linked in this study population. In contrast, Mati *et al*[8] in a cross-sectional study of 4404 women in Nairobi, observed a significant elevation in prevalence of cervical ectropion in OC users, but no significant association between ectropion and HIV risk. Similarly, Plourde *et al*[9] observed a higher prevalence of cervical ectropion in women currently using oral contraceptives but no association between the presence of cervical ectropion and prevalent HIV infection among 600 women attending an STD clinic.

STDs and OCs: Non-ulcerative and ulcerative STDs have been shown to be risk factors for HIV transmission in prospective studies.[10 11] Any STD that leads to inflammation or ulceration of the vulvar or vaginal epithelium may make the individual more vulnerable to HIV entry through these micro- or macro-mucosal lesions. The prevalence of chlamydial infection has been consistently observed to be increased among oral contraceptive users; the relation of OC's with other STD's is uncertain.[6]

Interference with menstrual bleeding pattern: Lymphocytes and macrophages are known target cells for HIV and are present in menstrual blood. Retrograde menstruation occurs in about 90% of women with normal fallopian tubes.[12] In this manner, HIV infected cells could reach areas well beyond the cervix including the mucosal surfaces of the uterus and tubes. Specific migratory macrophages that are susceptible to HIV infection have been identified in the genital mucosa.[13] OCs that contain both estrogens and progestins tend to decrease irregular bleeding and may protect against HIV. Contraceptive agents that contain progestational hormones only tend to induce irregular bleeding, which may increase risk of HIV transmission.

Specific local effects of progestins: Contraceptives that contain progestins only, such as the "mini pill" and the long-acting injectables

Table 1 Studies on the association between OC use and HIV infection

Author	*Type*	*Sample size*	*Comparison*	*RR (95% CI)*	*Controlled for at least one confounder*
Study population: STD clinic attenders					
Hitti 1992[21]	cross-sectional	1942	ever use/ never use	1·4 (1·1-1·7)	no
Plourde 1992[9]	cross-sectional	404*	> 12 mo use/ never use	1·2 (0·7-2·1)	yes
Pattulo 1992[20]	cohort	113	current/non -current	3·8 (1·1–13·4)	no
Study population: Family planning and antenatal clinic clients					
Bulterys 1990[25]	cross-sectional	961	ever use/ never use	5·0 (2·1-11·3)	no
Allen 1991[23]	cross-sectional	1458	ever use/ never use	1·4 (1·1-1·6)†	no
Mati 1991[22]	cross-sectional	4404	ever use/ never use	1·0 (0·7-1·8)	yes
Chao 1992[26]	cross-sectional	5288	ever use/ never use any method	3·9 (2·8-5·4)	yes
Kapiga 1993[24]	cross-sectional	2285	ever use/ never use any method	1·3 (0·9-1·8)	yes
Study population: couples					
Carael 1988[27]	case-control	288	OC in last 2 years	4·3 (1·4-15·4)†	no
Latif 1989[28]	case-control	150	current/ non-current	1·1 (0·4-1·2)	no
European Study Group 1989[29]	cross-sectional	155	current/ no method	1·4 (0·4-5·9)	no
Moss 1991[7]	cross-sectional	70	use since 1980/never use	2·9 (0·5-31·1)	no
Lazzarin 1991[30]§	cross-sectional	368	current/non -current	0·5 (0·3-1·0)	yes
Guimaraes 1992[32]	cross-sectional	204	use >1 yr /<1 yr	2·4 (1·1-5·3)	yes
Study population: commercial sex workers					
Darrow 1988[15]	case-control	640	?	1·0 (0·4-2·2)	no
Siraprasiri 1991[16]	cross-sectional	238	OC use/ non-use	0·7 (0·3-1·6)	no
Simonsen 1990[14]	cross-sectional	418	current/ non-current	2·2 (1·2-3·4)	yes
Plummer 1991[10]	cohort	196	ever/ never use	4·5 (1·4–13·8)	yes
Nzila 1991[17]	cross-sectional	1233	OC last 5 years/never use	1·3 (0·9-2·0)	no
Rehle 1992[18]	cross-sectional	356	ever use/ never use	1·5 (0·5-4·3)	yes
Laga 1993[11]	cohort	194	ever use/ never use	0·6 (0·2–2·4)	no

*Based on the 404/600 women in the study who did not give a history of prostitution.
†Association not significant when controlled for confounders.
§Data from Italian Partner Study.

and implants, could act on the risk of HIV transmission by at least two different mechanisms: thickening of the cervical mucus[12] and thinning of the vaginal epithelial layer.

Epidemiological evidence: Studies of the association between OC use and HIV infection are summarised in table 1. Unfortunately, most studies that are available are cross-sectional or case-control studies. With the exception of the study of Simonsen *et al*,[14] none of the cross-sectional studies that included female sex workers have reported a significant association between OC use and HIV seropositivity.[15-18]

Two studies have been conducted among STD clinic patients. Plourde *et al*[9] identified the long-term duration of oral contraceptive use as a significant predictor of HIV seropositivity. In the multivariate analysis, however, use of oral contraceptives remained a risk factor for HIV seropositivity only in women with concurrent genital ulcers. Nicolesi[19] points out that these findings must be interpreted with caution since the association between condom use and HIV infection in the multivariate analysis (OR 2·3, 95%CI 1·7–3·1) was somewhat stronger than the association between $\geqslant$12 months duration of oral contraceptive use and HIV infection (OR 1·1). Presumably, this was because the women in the study who gave a history of commercial sex work were more likely to use condoms, though few were completely protected. After removing these women from the analysis, the association between condom use and HIV disappeared, and the association between $\geqslant$12 months duration oral contraceptive use and HIV infection remained significant only in the presence of genital ulcers (OR 22·4, 95%CI 5·5–90·7). In a follow-up (mean 3·3 months) of 113 women attending the same STD clinic, 13 seroconverted.[20] Both cervical ectopy and OC use were significantly associated with seroconversion, however, only cervical ectopy was significant in a multivariate model.

In another study conducted in an STD clinic, Hitti *et al*[21] reported from Uganda that oral contraceptive use was associated with HIV seropositivity only in a subset of poor women. They point out that this association may well be a marker of unacknowledged high-risk sexual behaviour in these women.

In three of the studies that included low risk populations (clients in family planning clinics and antenatal clinics), no significant association between HIV infection and OC use was observed,[22-24] while in two,[25 26] significant positive associations were observed. In the largest of these studies for which full details are available, the relative risk for ever use of OCs was 1·0; the upper bound of the confidence interval excludes a large positive association, and no significant dose-response relation was seen between duration of OC use and risk of HIV infection.[22]

Studies that enrolled couples[7 27-32] have observed no consistent positive association between OC use and HIV serostatus. Moss *et al* conducted a cross-sectional study of HIV-seropositive men and their spouses in Nairobi, Kenya. OC use at study entry was not associated with HIV infection (OR = 0·4, 95% CI 0·01–7·0); however, the number of women reporting OC use was overall very small (12/70). In a multivariate analysis which included oral contraceptive use since 1980, the only independent predictor of HIV infection for spouses of HIV infected men was the presence of cervical ectropion. In the only study with a significant positive association,[27] no confounding factors were controlled for. In the Italian Partner Study,[30 31] the largest study of couples, a significant inverse association was observed between oral contraceptive use and HIV risk.

Plummer *et al*[10] conducted the largest of the two prospective studies among a cohort of 196 initially seronegative female prostitutes from a low socio-economic status area in Nairobi, Kenya. Of these women 124 were followed until seroconversion or for at least 12 months; 72 (36%) were lost to follow up. These authors observed an increased risk of HIV seroconversion among oral contraceptive users which persisted in a logistic regression model including average number of sex partners. This study is consistent with an independent role for OC use in facilitating infection by HIV among exposed women. However, the possibility of alternative explanations for the increased risk such as bias due to loss to follow-up or unmeasured confounding, means that further confirmation in other settings is required.

In the only other prospective study of sex workers, Laga *et al*[11] observed a reduced risk (RR = 0·6) of seroconversion associated with oral contraceptive use. The prevalence of OC use in this cohort was low however, thus the confidence intervals around the RR are wide and do not exclude a modest positive association.

In summary, we identified 21 studies that address the issue of oral contraceptive use and risk of HIV transmission. One of only two published prospective studies is the study with one of the highest relative risks for OC use. Results from cross-sectional studies are contradictory, perhaps due to different study populations (sex workers, family planning attenders, STD clinics clients), different classification of the OC exposure and the different extent to which studies were able to control for confounding. In studies which gave information on duration of oral contraceptive use, average duration of use was often short. If an aetiologic effect of OCs on HIV susceptibility exists, many months or years of use may be necessary to create the physiologic alterations responsible; few studies have included substantial numbers of women with long durations of OC use.

Injectable Hormones

Mechanisms of influence of HIV transmission: Depo-provera (medroxyprogesterone), the most commonly used injectable, is a progestational zenohormone. Women using Depo-

Table 2 Studies on the association between use of injectable hormones and HIV infection.

Author	*Type*	*Sample size*	*Comparison*	*RR (95% CI)*	*Controlled for at least one confounder*
Nzila 1991[17]	cross-sectional	1233	ever in last 5 years/ never use	1·0 (0·5-2·1)	no
Allen 1991[23]	cross-sectional	1458	ever use/ never use	1·4 (1·1-1·9)	no*
Mati 1991[22]	cross-sectional	4404	current/non -current	1·2 (0·7-2·1)	yes
Plourde 1992[9]	cross-sectional	600	ever use/ never use	2·7 (1·0-7·2)	no
Rehle 1992[18]	cross-sectional	356	current/no method	2·9 (1·0-7·9)	yes
Kapiga 1993[24]	cross-sectional	2285	ever/no method	1·8 (0·8-4·2)	yes

*Association not significant when controlled for confounders.

provera report menstrual irregularities, such as spotting or prolonged periods of bleeding, which could theoretically increase risk of HIV transmission. Medroxyprogesterone could also cause enhanced vulnerability of the vaginal epithelium through thinning of this tissue and thus facilitate transmission of HIV and other STDs through superficial lesions.

As Depo-provera is administered by intramuscular injection, use of non-sterile needles might be accompanied by HIV transmission. However, in many countries, Depo-provera is provided in single-use, disposable syringe packs.

Epidemiological evidence: Few studies have investigated the association between injectable hormones and HIV infection, perhaps because the overall prevalence of Depo-provera use in developing countries is low (see Table 2). All available studies are cross-sectional and although several studies observed positive associations between use of injectable hormones and HIV seropositivity, many of these associations were of borderline significance. The strongest association was observed by Rehle *et al*[18] (RR 2·9, 95%CI 1·0–7·9), but was based on a sample of only 77 women using injectable hormones, 11 of whom were HIV positive.

It is not possible to draw conclusions about the association between injectable hormone use and risk of HIV transmission from the available data. Further exploration of this issue is urgent owing to the increasing use of this contraceptive method in areas of high HIV prevalence.

Table 3 Studies on the association between IUD use and HIV infection.

Author	*Type*	*Sample size*	*Comparison*	*RR (95% CI)*	*Controlled for at least one confounder*
European Study Group 1989[29]	cross-sectional	155	current use/ no method	2·0 (0·4-10·9)	no
Lazzarin 1991[30]*	cross-sectional	368	current/ non-current	3·1 (1·4-7·1)	yes
Mati 1991[22]	cross-sectional	4404	current/ non-current	1·5 (0·6-3·7)	yes
Plourde 1992[9]	cross-sectional	600	ever use/ never use	0·6 (0·2-1·7)	no
Kapiga 1993[24]	cross-sectional	2285	ever use/ never use	2·5 (1·4-4·6)	yes

*Data from Italian Partner Study.

Intrauterine Devices (IUDs)

Over 90 million women worldwide are now using IUDs and the prevalence of IUD use worldwide can be expected to increase.[33] The evidence that IUDs are associated with upper reproductive tract infections has been found to be weaker than previously thought.[13 34] However, even in the absence of infection, IUDs cause an inflammatory response and infiltration of leukocytes, and epithelial ulceration in the uterine mucosa.[35]

Postulated mechanisms of increased risk of HIV in IUD users are the mobilisation of macrophages in the endometrial layer of the uterus that become targets for HIV infection, and the increased bleeding associated with IUD use.[36] Few studies specifically address the relationship between IUDs and HIV transmission, mostly due to the low prevalence of IUD use in the areas of the world with the highest prevalence of HIV infections. Those that have been done are cross-sectional in design and all, with the exception of the study by Plourde *et al*,[9] have reported an increased risk of HIV seropositivity associated with IUD use (see table 3). However, this association must be further investigated in prospective studies.

Spermicides

Spermicides have been widely recommended for the prevention of HIV transmission since nonoxynol-9, the active ingredient in most commercially available spermicide preparations, was shown to inactivate HIV in laboratory studies[37–39] and condoms impregnated with nonoxynol-9 were shown to provide an effective chemical barrier to HIV even after breakage.[40]

Nonoxynol-9 is a nonionic surfactant that acts by disrupting cell membranes and viral envelopes. Randomised clinical trials have confirmed that the use of nonoxynol-9 preparations decreases the transmission of chlamydial, gonococcal, and trichomonas infections,[41–44] all of which have been shown to be independently associated with increased risk for the transmission of HIV.[10 11] In a meta-analysis of 65 studies of the effect of barrier contraceptives on STD risk, Rosenberg *et al*[45] found a decreased risk for chlamydia, gonorrhoea, and trichomoniasis associated with the use of spermicide containing contraceptives compared to no method (RR = 0·52, 95% CI 0·51–0·53).

Clinical trials of the effect of nonoxynol-9 on HIV transmission are limited. Kreiss *et al*[46] randomly assigned 138 commercial sex workers in Nairobi, Kenya to use either a nonoxynol-9 sponge or a placebo vaginal suppository in addition to condoms with each sex partner. Fifty seven women developed HIV antibodies during the course of the study. Use of the nonoxynol-9 sponge increased the risk of genital ulcers (RR = 3·3, $p < 0·001$) and vulvitis (RR = 3·3, $p < 0·001$) during follow-up, and decreased the risk of gonococcal cervical infection (RR = 0·4, $p < 0·001$). The nonoxynol-9 sponge group had a slightly increased risk of HIV seroconversion (RR = 1·6, 95% CI 0·8–2·8).

Table 4 Studies of nonoxynol-9 toxicity.

Author	Type of study	Number of subjects	Dose	Epithelial disruption (Prevalence with 95% CI)
Niruthisard 1991[50]	Phase I toxicity study*	14	150 mg suppositories	43% (18–71%)
Roddy 1993[51]	Clinical trial	175	150 mg suppositories	
			Group I: once every other day	18% (7–35%)
			Group II: once daily	34% (19–52%)
			Group III: twice daily	29% (15–47%)
			Group IV: 4 times a day	53% (35–70%)
			Group V: placebo	15% (5–31%)

*Women inserted one suppository per hour for 4 consecutive hours each day and waited one hour after the last insertion before washing or douching with water.

The Nairobi sponge trial is contradicted by two other prospective studies in Africa. The first, involving 273 commercial sex workers in Cameroon,[47] found that consistent use of nonoxynol-9 suppositories decreased the risk of HIV seroconversion after adjusting for condom use (RR = 0·1, 95% CI 0·1–0·6). In contrast to the Nairobi study, the Cameroon study found a non-significantly lower incidence of genital ulcers among consistent spermicide users. The other African prospective study was conducted among HIV discordant couples in Zambia. Consistent nonoxynol-9 suppository use was protective against HIV seroconversion in initially seronegative women (RR = 0·6).[48]

Toxicity/mucosal damage: A possible explanation for these seemingly contradictory findings is that the protective effect of the direct action of nonoxynol-9 on HIV itself may be countered by damage to the vaginal and cervical mucosa, paradoxically enhancing HIV transmission.

Even after controlling for the increased baseline prevalence of genital ulcer disease, there was a significantly increased risk of developing genital ulcers in the nonoxynol-9 sponge group in the Nairobi study. One question is whether this increased risk was due to the chemical effect of nonoxynol-9 or the physical effect of the sponge itself.[49] Research comparing different delivery vehicles for nonoxynol-9 has yet to be reported. On the other hand, the fact that increased risk of ulcers was significant only in the vulvar area (RR = 3·5, p = 0·003 for vulvar ulcers; RR = 2·0, p > 0·05 for vaginal/cervical ulcers) argues against a direct mechanical effect of the sponges.

In addition, the women in the Nairobi study used an average of 14 sponges (each containing one gram of nonoxynol-9) per week, an unusually high dose. In contrast, 100 mg nonoxynol-9 suppositories were used in the Cameroonian study[47] (mean number of sexual partners per week = 4·7) and no increase in genital ulcers was seen. Vaginal and cervical mucosal damage has been observed with nonoxynol-9 in other studies and the toxic effect of nonoxynol-9 appears to be dose-related[50 51] (table 4). In the previously mentioned studies of nonoxynol-9 in the prevention of STDs, there was no reported increased risk of genital ulcers.[41–44 48] However, some of these studies showed an increased risk of candidal infections[41 52] or vaginal irritation.[42]

Prospective studies are needed to further clarify whether nonoxynol-9 increases or decreases a woman's risk of HIV seroconversion. In particular, the effect of different levels of use (dose) must be explored, as well as the effect of different vehicles for delivery of spermicidal agents, including the effects (for example change in vaginal Ph) of inactive ingredients.

Other spermicidal agents: Although nonoxynol-9 is the most widely available and most extensively studied spermicide, other spermicidal compounds have been shown to inactivate HIV and other sexually transmitted disease pathogens.[53 54] Chlorhexidine has been shown to enter and remain active in cervical mucous at concentrations found in vaginal secretions,[54 55] a property that may make it more effective in vivo than nonoxynol-9 which is inactivated by cervical mucous. Other spermicidal preparations that show activity against HIV in vitro but are not currently approved for use include Betadine, menfegol, and gossypol. The only in vivo study of these compounds to date is a Phase I clinical trial of menfegol which was stopped due to excessive epithelial toxicity.[56]

The Contraceptive Research and Development (CONRAD) Program is currently searching for new spermicides, but progress is slow. One hundred and thirty one potentially spermicidal compounds were screened in 1992 for in vitro activity against HIV. Twenty six were found to inhibit HIV and several of those are being tested for toxicity in animal models.[54]

The Female Condom

The female condom consists of a soft, loose-fitting polyurethane sheath with a flexible ring at each end. The outer rings covers the vulvar mucosa, in contrast to previously available barrier methods which leave the vaginal and vulvar mucosa unprotected.

The major questions about the effectiveness of the female condom in the prevention of the transmission of HIV are its efficacy as a physical barrier, its durability and performance during use, and most importantly, its acceptability and availability. As Stein[2] notes, an efficacious barrier method that is not consistently utilised by high-risk populations will not interrupt the transmission of disease. On the other hand, a less efficacious barrier that is more frequently used could possibly play a more important role in the prevention of disease.

Efficacy: Although a latex sheath and latex pouch have also been developed, only the polyurethane sheath has been extensively tested and is available commercially. However, there are no clinical studies of its effectiveness in the prevention of HIV transmission. In vitro studies have shown that intact polyurethane condoms are an effective

barrier to cytomegalovirus and human immunodeficiency virus,[57] as well as herpes virus and/or hepatitis B virus and gas and dye particles smaller than HIV.[58] There is only one in vivo study of the efficacy of the female condom in the prevention of STD. In a small prospective study of 104 women treated for trichomonas vaginitis in urban gynecology clinics in the US, there were no recurrences of trichomonas over the six week study period in the 20 women who used the female condom consistently with every sexual encounter compared to a 14% (7/50) recurrence rate for trichomonas in the non-barrier group ($p = 0{\cdot}08$), and a 15% (5/34) recurrence rate among the inconsistent users of the female condom ($p = 0{\cdot}09$).[59] This study underscores the previous assertion that the consistency of barrier method use determines the effectiveness of even the most efficacious barriers.

A single study of the effects of the female condom on the vaginal and vulvar mucosa comparing the female condom to the diaphragm (both used without spermicides) showed no evidence of trauma and no change in vaginal flora due to the female condom.[60] No serious side-effects or allergies to the polyurethane female condom have been reported to date.[61]

Durability and Performance: Clinical studies suggest that the polyurethane female condom is more durable and less likely to break than latex male condoms. In studies of the "Reality" brand condoms sponsored by the manufacturer (Wisconsin Pharmacal Co.), only 0·6% (3/521) of female condoms leaked after being used for one act of intercourse when tested by the standard ASTM water leak test. Under the same conditions, 3·5% (18/516) of male condoms leaked ($p < 0{\cdot}001$). Using questionnaires to determine the rate of vaginal exposure to semen due to either slippage or tears in 50 couples, the female condom was again superior (2·7% vs. 8·1%, $p = 0{\cdot}03$). This was confirmed by vaginal swabs in 15 women (after 5 episodes of intercourse each) in which no evidence of sperm was found (95% CI 0–4·5%).[62] Overall, breakage rates in studies of the polyurethane female condom range from 0 to 9%, compared with 0 to 12% for the latex male condom.[63]

Other studies[64–67] have suggested higher rates of problems with the use of the female condom, including frequent slippage of the outer ring into the vagina, the penis entering between the outer ring and vaginal wall (effectively missing the condom), and the condom slipping out of position. Such problems were reported in 4–10% of female condom uses in a study of Kenyan family planning clinic attenders.[64]

Acceptability: Studies of the acceptability of the female condom to date give widely varying results according to the country in which they are conducted, the population studied and the means of recruiting and educating study subjects (see table 5). Most women who found the condom unacceptable rejected it because of physical discomfort or objections to the appearance or noise of the condom. The introduction of the female condom into sex worker populations did not necessarily empower the women to use them. Despite having the option of both the male and female condoms, CSWs in Thailand and Cameroon still reported multiple episodes of unprotected sex.[65 68]

Although over 40% of the male partners of the women in most studies also liked the female condom or were neutral toward it, this is an overestimate of the true rate of male acceptance since women whose partners disliked the female condom were more likely to drop out of the studies.[64 68] Furthermore, the substantially higher cost of the female condom compared with the male condom will almost certainly restrict its availability.

In summary, the available data suggest that the female condom has a place in the array of available barrier contraceptives, but it is not the final answer to the need for a female-controlled method. There is a subgroup of women who prefer the female condom and are able to negotiate its use with their partners. However, acceptability studies show that there is also a substantial subgroup of women who, while initially interested in a barrier method under female control, find the female condom unacceptable. More methods need to be developed to offer further options so that all women can find a protective method that meets their needs.

Table 5 Studies of the acceptability of the female condom

Country	*Population*	*N (F)*	*Dropout Rate*	*%female like or neutral (based on number who answered)*	*%male like or neutral (based on number who answered)*
Kenya[64]	couples	48	75%	89% (34/38-Phase I) or 100% (12/12 at end of Phase II)	47% (18/38) Phase I
Cameroon[65]	CSWs	38	11%	94% (32/34)	59% (20/34)
UK*[66]	volunteers	106	33% (at 1 month) 55% (at 3 month)	43% (46/106 at last interview)	42% (44/106 at last interview)
Thailand[68]	CSWs	20	0%	66%	—
Mexico[69]	CSWs	24	25%	—	—
Denmark[70]	couples	20	0%	100%	100%‡
Thailand[67]	couples	18	28%†	62%	15%

*Study terminated prematurely due to supply of condoms. 11/106 (10%) completed > 12 mo and 20/106 (19%) terminated prematurely at 3–11 mo.
†Of 56 women shown the female condom and responding to the initial questionnaire, only 18 agreed to participate in the study.
‡Most of the women reported acceptance of the female condom by male clients.

Research Priorities

Many unanswered questions on the associations between specific contraceptive methods and HIV transmission remain and at least two different kinds of approach are necessary: prospective epidemiological studies and basic research.

There is an urgent need for more prospective epidemiological studies. In order to settle the question of whether there is an association between individual contraceptive methods and HIV infection, well-designed

studies that specifically address these questions are warranted. Large studies involving low risk women using contraceptives for extended periods are necessary to evaluate the impact of contraceptive use among the majority of users. The possibility of behavioural differentials between users of different contraceptive methods needs to be carefully studied.

Through basic research, we need to know more about the sites of virus entry, infectivity, and local defence mechanisms in the female genital tract. To target the heterosexual transmission of HIV effectively, it is crucial to learn more about mucosal immunity mechanisms, physiological changes during the menstrual cycle, and the effect of hormonal contraceptives on these mechanisms.

Clinical testing of spermicidal preparations other than nonoxynol-9 that have been found to be effective and nontoxic in laboratory studies is urgently needed and the development of new non-contraceptive virucides to separate HIV prevention from family planning is also desirable. The latter depends on further research to determine whether HIV is actually transmitted by the sperm itself, although the current consensus is that sperm does not carry HIV.[54]

In the case of the female condom, further design modifications are necessary to achieve a product that is less noticeable, more comfortable, quieter, and easier to insert. As the female condom is considered for use in developing countries, it will be important to test the effect of repeated uses and the effect of heat and long periods of storage on the integrity of the condom.

Important issues for family planning services

The HIV epidemic is forcing family planning services to incorporate discussion of the risk of HIV infection into their counselling regarding the risks and benefits of various contraceptive methods. Since both family planning programmes and AIDS control programmes deal with the highly sensitive issue of sexuality and with protection from the undesired effects of intercourse, they are well-placed to work together. In countries with the highest prevalence of HIV, even women who are traditionally considered at low-risk of infection (for example pregnant women or family planning clinic attenders), have prevalence rates >5%.[22 23 71] Family planning clinics offer an opportunity to reach this vulnerable sector of the population.

Based on the currently published literature, no firm conclusions regarding the increased or decreased risk of HIV transmission associated with specific contraceptive methods (with the exception of the male latex condom) can be drawn. Because of the uncertainty associated with the effect of individual female methods of contraception on HIV transmission, counselling women regarding contraceptive method choice must continue to be based primarily on STD and pregnancy prevention. Although male condoms are still considered the best protection against HIV, they have a high contraceptive failure rate. Unfortunately, this requires the use of two methods of contraception, one for pregnancy prevention and the other for HIV prevention. This effort is only sustainable by a woman/couple with a high level of motivation. The problem is especially acute for HIV seropositive women who not only want to prevent infection of their partners, but may wish to prevent pregnancy because of the high probability of vertical transmission.

At this point in the AIDS epidemic, the prevention of the heterosexual transmission of HIV is of paramount importance. Women all over the world are at risk for HIV, even within marital relationships. Protective methods that are under the control of women and that are acceptable to men must be developed and made available.[2 72] More information on the effect on HIV transmission of conventional methods is long overdue. Considering that contraceptive use is being promoted worldwide, including in areas where HIV incidence is increasing, further knowledge regarding the effect of individual contraceptives on HIV transmission is imperative.

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